PATENT ABSTRACTS OF JAPAN

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(54) HEMOFERRUM-CONTAINING COMPOSITION FOR ORAL

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a composition which enables the effective absorption of hemoferrum without being largely affected by gastric acid.
SOLUTION: This hemoferrum-containing composition for oral is prepared in an enteric form, and the hemoferrum-containing composition for oral contains the hemoferrum coated with an enteric substance.

Claims

[Claim(s)]

[Claim 1]An enteric-coated-preparation-ized constituent for hemoferrum content taking orally.

[Claim 2]A constituent for hemoferrum content taking orally containing hemoferrum covered with an enteric substance.

[Claim 3]The constituent for hemoferrum content taking orally according to claim 2 whose enteric substance is one or more sorts chosen from zein, a shellac, and sodium alginate.

[Claim 4]A constituent for hemoferrum content taking orally given in any 1 paragraph of Claims 1-3 which is a gestalt of a capsule, a tablet, or powders.

[Claim 5]A constituent for hemoferrum content taking orally given in any 1 paragraph of Claims 1-4 which is foodstuffs.

Detailed Description

[Detailed Description of the Invention]

[0001]

[Field of the Invention]This invention belongs to the field of a hemoferrum containing composition.

[0002]

[Description of the Prior Art]In recent years, 50% of adults are permitted a woman's ischemia, and it has attracted attention from a viewpoint of alimentation as a trouble peculiar to a woman. Since spread, an unbalanced diet, etc. of junk food become a cause and ischemia's [a male] are increasing these days, ischemia is SUBJECT which cannot be disregarded on nutrition. About supply of iron, the hemoferrum which has in iron the structure which hem protein combined rather than inorganic iron from a viewpoint of absorption efficiency is used for the health food aiming at an anemic improvement, prevention, etc. from absorption being good. As main manufacturing methods, an ultrafiltration method and an isoelectric point sedimentation method are established, and the hemoferrum can be manufactured industrially. However, the physicochemical qualities of the hemoferrum which is both a method and was manufactured differ. That is, it is reported from the absorption test in the in vitro level which was with the solubility to water, the solubility at the time of fluctuating pH of water, and a reversal intestinal tract, etc. that there is a difference of absorption efficiency. Thus, various researches to which the hemoferrum raises absorption efficiency are done.

[0003]However, it is known that protein will receive denaturation in acid or alkali. Since the hemoferrum was also the gestalt which heme protein combined with iron, when taken in by the living body, denaturation by gastric acid is received, the original character of the hemoferrum is lost in the small intestine which is an absorption part, and it began to be pointed out that absorption worsens.

[0004]In order to solve this phenomenon, it is a problem of the structure itself which iron has combined, the background, i.e., the hem protein, on the theory that not the problem that can be coped with only by solution by the conventional hemoferrum manufacturing method but the hemoferrum has, and that absorption efficiency is good.

[0005]

[Problem(s) to be Solved by the Invention]The problem of the structure itself which iron has combined, the background, i.e., the hem protein, on the theory that the hemoferrum has and that absorption efficiency is good, is solved, and the original character of the hemoferrum is not lost, but this invention makes it the SUBJECT to provide the constituent

for hemoferrum content taking orally with sufficient absorption.

[0006]

[Means for Solving the Problem]When it was possible for this invention person to have made hemoferrum reach to intestines in the state where it is not influenced by gastric acid, absorption of hemoferrum in an intestinal tract increased, found out that the feature of hem protein which hem protein and iron combined was improvable from a viewpoint of improvement in absorption efficiency, and completed this invention.

[0007]Namely, a constituent for hemoferrum content taking orally which this invention formed into 1. enteric coated preparation, 2. Constituent for hemoferrum content taking orally containing hemoferrum covered with enteric substance, 3. An enteric substance is one or more sorts chosen from zein, a shellac, and sodium alginate. It is related without any one constituent for hemoferrum content taking orally of the above 1-4 which is any one constituent for hemoferrum content taking orally of the above 1-3 which is a gestalt of a constituent for hemoferrum content taking orally of the above 2, 4. capsule, a tablet, or powders, and 5. foodstuffs.

[0008]

[Embodiment of the Invention]Enteric coated preparation-ization of this invention carries out enteric coating of the hemoferrum content tablet, it can carry out to adopting enteric coated preparation-ized art, such as using an enteric multilayered tablet and filling up an enteric capsule with the hemoferrum, and can also carry out by covering the hemoferrum with an enteric substance and pharmaceutical-preparation-izing it to a tablet, powders, a capsule, etc. further.

[0009]The substance in which the enteric capsule is known as an ingredient which controls the solubility in gastric acid to a seam capsule, a seamless capsule, a hard capsule, etc., For example, the thing to do for the coat of a shellac, zein, and the sodium alginate (for example, refer to JP,H11-302158,A), Or a capsule substrate is made to contain casein, sodium alginate, etc., It can manufacture by processing into a hard capsule forming a capsule (refer to JP,H2000-63289,A) and the substance known as an ingredient which controls the solubility in gastric acid, for example, chitosan, etc.

[0010]The substance known as an ingredient which controls the solubility in gastric acid, for example, a shellac, zein, sodium alginate, and chitosan can perform coating of a tablet. For example, an enteric coated tablet can be manufactured by the method of spraying the ethanol solution which contains a shellac after tableting the hemoferrum on a tablet surface.

[0011]These pharmaceutical preparation-ization can be performed by adopting the art in which it is used for manufacturing the usual enteric coated preparation.

[0012]In this invention, the coating of the ingredient which does not dissolve with gastric acid

but dissolves by an intestinal tract, i.e., an enteric substance, a shellac, zein, and the sodium alginate may be directly carried out to the hemoferrum, and it may be processed so that gastric acid tolerance may be given and it may dissolve by an intestinal tract. In this case, the way the coating method sprays the ethanol solution which contains a shellac, for example at the time of the granulation of the hemoferrum is raised. It is preferred to use a food composition with gastric acid tolerance as a substance used for coating of such hemoferrum.

[0013]In this method, the coated hemoferrum is processible into solid preparations, such as a capsule, powders, and a tablet. As foodstuffs, it is processible into capsule type foodstuffs, powdered food, tablet type foodstuffs, a hard candy, etc. That is, processing for various foodstuffs is possible for the hemoferrum which carried out the coating of the food composition which has gastric acid tolerance in the hemoferrum itself, and it does not receive restriction of the gestalt of foodstuffs.

[0014]Even if any of the hemoferrum which also manufactured the hemoferrum manufactured with the marginal filtration process with the isoelectric point sedimentation method are used for the hemoferrum used by this invention, it does not interfere. However, since the direction of what the absorption efficiency in intestines depends on an ultrafiltration method is excellent, it is preferred to use the hemoferrum manufactured by the ultrafiltration method.

[0015]Without receiving denaturation by gastric acid, since the hemoferrum which performed the above processings reaches to intestines, it can demonstrate the absorption superior to the inorganic iron which the hemoferrum originally has, and can raise the absorption efficiency to the inside of the body.

[0016]The constituent of this invention can contain addition ingredients by which normal use is carried out in pharmaceutical-preparation-izing, such as an excipient, a binding material, disintegrator, and lubricant.

[0017]Specifically Milk sugar, dextrin, starch, gum arabic, xanthan gum, Tragacanth gum, pullulan, grape sugar, fructose, maltose, sorbitol, Mannose, fructose, sugars like xylose, cellulose, Casein sodium, gelatin, albumin, soybean protein, protein like wheat gluten, Calcium phosphate, calcium carbonate, magnesium stearate, refining talc, Sucrose fatty acid ester, polyglyceryl fatty acid ester, fatty acid alkali metal salt, Lauryl sulfate alkali metal salt, aliphatic amino acid, aromatic amino acid, heterocyclic amino acid, boric acid, adipic acid, fumaric acid, succinic acid, benzoic acid alkali metal salt, sodium sulfate, a polyethylene glycol, and vegetable hydrogenated oil can be used.

[0018]These pharmaceutical preparation-ization can be performed by adopting the usual pharmaceutical preparation art. For example, in the case of a tablet and a hard candy, after

making into granularity by a suitable method what mixed uniformly the hemoferrum covered with the hemoferrum or an enteric substance and an excipient, a binding material, disintegrator, or other suitable additive agents, compression molding of the additive agent in which others are [being lubricant and] suitable is added and carried out. Or compression molding of what mixed uniformly the hemoferrum covered with the hemoferrum or an enteric substance and an excipient, a binding material, disintegrator, lubricant, or other suitable additive agents can be carried out directly, and it can be manufactured.

[0019]In the case of a capsule, after making into granularity by a suitable method what mixed uniformly remaining as it is or an excipient, a binding material, disintegrator, or other suitable additive agents for the hemoferrum covered with the hemoferrum or an enteric substance, for example, encapsulation of the additive agent in which others are [flow being an accelerator and] suitable is added and carried out. To the hemoferrum covered with the hemoferrum or an enteric substance, or an excipient, a binding material, Add the hemoferrum and flow accelerator which were covered with the hemoferrum or an enteric substance to the granulation which filled up the capsule with what mixed uniformly disintegrator, a flow accelerator, or other suitable additive agents directly, and manufactured it, or was manufactured beforehand, and as it is, Or encapsulation is carried out, after adding a suitable additive agent and mixing uniformly.

[0020]Carrier fluid is used for powders by using as a raw material the hemoferrum coated with the enteric substance, and they manufacture it with a conventional method using commercial granulators (for example, Fuji Paudal make etc.). The fluidized bed granulation method which specifically uses a fluidized bed granulator, the stirring granulation method which uses a stirring granulator, the rolling granulation method which uses tumbling granulator, etc. can be illustrated. Although the substance of a drainage system and the substance of a non-drainage system can be used as carrier fluid used, when the physical properties of the hemoferrum and the use as food preparation are taken into consideration, it is desirable to use natural oil fat.

[0021]Into a hemoferrum content oral composition, vitamins, such as vitamin B2, vitamin B6, vitamin B12, pantothenic acid, biotin, folic acid, vitamin C, and vitamin E, can also be blended.

[0022]It is preferred to make the hemoferrum more specifically contain 9.5% 4 to 10% by weight conversion in an oral composition. Although an oral composition is hemoferrum equivalent weight per one person and can more specifically be prescribed for the patient 63 mg 30-70 mg on the 1st, it can set up a dose suitably according to an applied object, its condition, etc.

[0023]

[Example]Test result 1 [influence of gastric acid on absorption of heme iron]
The next experiment was conducted in order that gastric acid might check influence on absorption of the hemoferrum. The experimental method administered orally the hemoferrum of the respectively same quantity as the rat which does not control gastric-acid secretion, and the rat which controlled secretion of gastric acid using the stomach tube, and compared it after [5 and 15] administration and about serum iron for 30 minutes.
[0024]Test-method hemoferrum It prepared to the concentration of 2 mg/mL with distilled water. The animal was distributed to three groups of one groups [five] so that a difference might not appear in weight using 15 4-week old SD system rats. Group setting out set up a total of three groups of a gastric-acid secretion group, a gastric-acid secretion control group, and a distilled water administration group. Control processing of gastric-acid secretion was performed after the end of a group division. The dose of the hemoferrum was made into 1 mg/kg, the stomach tube was used and administration was performed once by the dosage of 0.5 mL/kg, after each group abstained from food for 20 hours. Heparin sodium ******** was used and each group performed blood collecting temporally from the jugular vein after [5 and 15] administration and in 30 minutes. Centrifugality of the extracted blood was carried out on the conditions for 4 **, and 1500 G or 10 minutes, and it separated plasma. The parameter used absorption of the hemoferrum as serum iron (concentration, mug/dL) which is a parameter reflected directly, and measurement was performed by the Nitroso-PSAP method. The statistical work computed average value and standard deviation about serum iron, and performed comparison for every blood collecting time of a gastric-acid secretion group and a gastric-acid secretion control group by F-t assay which considered the gastric-acid secretion group as contrast. A result is shown in Table 1.
[0025]
[Table 1]

表 1 血清鉄（濃度、μg/dL， n=5，平均値±標準偏差）

設定群	投与後 5 分	投与後15分	投与後30分
胃酸分泌群 1mg/kg	137.4±5.89	176.4±5.78	291.0±8.02
胃酸分泌抑制群 1mg/kg	149.2±6.88*	212.4±8.52*	302.8±5.03
蒸留水投与群 (－)	96.8±5.78	98.0±4.69	98.8±2.86

F －t 検定：＊p<0.05

[0026]Since serum iron of the distilled water administration group was almost equivalent and

was changing, the influence on serum iron by blood collecting with the passage of time in this experiment was not accepted. Serum iron of the gastric-acid secretion group and the gastric-acid secretion control group shows the high price from the distilled water administration group, and absorption of the hemoferrum was accepted for both groups. On the other hand, comparison of a gastric-acid secretion control group and a gastric-acid secretion group showed after administration the increase in which serum iron of a gastric-acid secretion control group is more significant than a gastric-acid secretion group in 5 or 15 minutes, and absorption of the hemoferrum had the high gastric-acid secretion control group.

[0027]As for the above result, gastric acid shows that absorption of the hemoferrum worsens and it is shown by by protecting the hemoferrum from gastric acid that absorption of heme iron is improved.

[0028]Test result 2 [enteric capsule heme iron absorption test]

The shellac coating hard capsule which enclosed the hemoferrum of the quantity with the respectively same experiment. It carries out by administering orally to an adult male the hard capsule (henceforth a hard capsule) which dissolves with (it is hereafter called an enteric capsule) and the stomach which is not coated, and comparing after [30 and 60] administration and serum iron for 180 minutes. The empty capsule presentation of an enteric capsule and a hard capsule is shown in Table 2.

[0029]

[Table 2]

表2　空カプセル組成成分

成　分	ハードカプセル	腸溶性カプセル
ゼラチン	84.0～88.0%	84.0～88.0%
水　分	12.0～16.0%	12.5～15.3%
シェラック	－	0.5～0.7%

[0030]The experimental method hemoferrum was prepared so that an enteric capsule and a hard capsule might serve as a content of 15.75 mg / capsule using the No. 3 capsule. The test subject was taken as five healthy adult men aged from 26 to 39.

[0031]An experiment is conducted on the crossover of an enteric capsule and a hard capsule, and first, an enteric capsule is performed as the experiment 1 and then it prescribes a hard capsule for the patient as the experiment 2. The interval of the experiment 1 and the experiment 2 was made into two weeks. A dose is used as one-person four capsules (63.0 mg/man), and after administration abstains from food for 12 hours, it carries out single-dose administration of the four capsules, and carries out drinking water of the distilled water

200mL to immediately after. Blood collecting is performed before administration, after [30 and 60] administration, and in 180 minutes. Centrifugality of the extracted blood was carried out on the conditions for 4 **, and 1500 G or 10 minutes, and it separated the blood serum. A parameter uses absorption of the hemoferrum as serum iron (concentration, mug/dL) which is a parameter reflected directly, and measurement is performed by the Nitroso-PSAP method. The statistical work computed average value and standard deviation about serum iron, and performed nonparametric processing. A result is shown in Table 2.

[0032]

[Table 3]

表3 血清鉄(濃度、μg/dL, n=5, 平均値±標準偏差)

実 験 (ヘム鉄量)	投与前	投与後30分	投与後60分	投与後 180分
実験1 腸溶性カプセル (63.0mg/人)	131.6± 24.6	154.6± 35.2*	164.± 48.3*	148.6± 50.9
実験2 ハードカプセル (63.0mg/人)	134.4± 25.2	145.2± 40.6	151.0± 40.3	146.9± 45.8

Wilcoxon test : *p<0.05

[0033]Since there is no difference in serum iron before administration of the experiment 1 and the experiment 2, it is shown that there is no resldual effect of the experiment 1 in the experiment 2 which opened and carried out the interval of two weeks.

[0034]Serum iron after administration is increasing both experiments from administration before, and absorption of the hemoferrum is shown for the administration using the hard capsule of administration and the experiment 2 using the enteric capsule of the experiment 1. On the other hand, by the comparison, serum iron of the experiment 1 shows a high price rather than the experiment 2 after [30 and 60] administration and for 180 minutes. Especially, by after-administration 30 or 60 minutes, it is a significant difference and the absorption improvement of the hemoferrum by an enteric capsule is shown.

[0035]Test result 3 [absorption test of an enteric covering hemoferrum tablet]

An experiment is conducted by administering orally to an adult male the tablet (henceforth a shellac tablet) which carried out the shellac coat containing the hemoferrum of the respectively same quantity, and the tablet (henceforth a common tablet) which does not carry out a shellac coat, and comparing after [30 and 60] administration and serum iron for 180 minutes. The latch agent presentation of a shellac tablet and a common tablet is shown in

Table 4.

[0036]

[Table 4]

表 4　空錠剤組成成分

成　分	一般錠剤	腸溶性錠剤
でんぷん	84.0～88.0%	84.0～88.0%
なたね油脂末	12.0～16.0%	12.0～16.0%
シェラック	－	0.5～0.7%

[0037]The experimental method hemoferrum was prepared so that it might become a content of 15.75 mg/a lock per dose, and it was used for it as a shellac tablet, having carried out the shellac coat of the initial complement. The test subject was taken as five healthy adult men aged from 26 to 39. An experiment is conducted on the crossover of a shellac tablet and a common tablet, and first, a shellac tablet is performed as the experiment 1 and then it prescribes a common tablet for the patient as the experiment 2. The interval of the experiment 1 and the experiment 2 was made into two weeks. A dose is made into 4 doses (63.0 mg/man) per person, and after administration abstains from food for 20 hours, it carries out single-dose administration of the 4 doses, and carries out drinking water of the distilled water 200mL to immediately after. Blood collecting was performed before administration, after [30 and 60] administration, and in 180 minutes. Centrifugality of the extracted blood was carried out on the conditions for 4 **, and 1500 G or 10 minutes, and it separated the blood serum. The parameter used absorption of the hemoferrum as serum iron (concentration, mug/dL) which is a parameter reflected directly, and measurement was performed by the Nitroso-PSAP method. The statistical work computed average value and standard deviation about serum iron, and performed nonparametric processing. A result is shown in Table 5.

[0038]

[Table 5]

表5 血清鉄（濃度、μg/dL，n=5，平均値±標準偏差）

実　験 （ヘム鉄量）	投与前	投与後30分	投与後60分	投与後 180分
実験1 シェラック錠剤 （63.0mg/人）	136.4± 23.1	153.5±32.6*	162.8±40.8*	143.2± 40.2
実験2 一般錠剤 （63.0mg/人）	134.6± 22.9	140.3±40.8	145.0±40.6	140.5± 50.4

Wilcoxon test：＊p<0.05

[0039]Since there is no difference in serum iron before administration of the experiment 1 and the experiment 2, it is shown that there is no residual effect of the experiment 1 in the experiment 2 which opened and carried out the interval of two weeks.

[0040]Serum iron after administration is increasing both experiments from administration before, and absorption of the hemoferrum is shown for administration of the shellac tablet of the experiment 1, and administration of the common tablet of the experiment 2. On the other hand, by the comparison, serum iron of the experiment 1 shows the high price rather than the experiment 2 after [30 and 60] administration and for 180 minutes. In particular, by after-administration 30 or 60 minutes, it is a significant difference and the absorption improvement of the hemoferrum by a shellac tablet is shown.

[0041]Thus, by enteric-coated-preparation-izing the hemoferrum shows that iron absorption increases in internal use. Therefore, the constituent of this invention is useful to the anemic improvement and prevention which were hard to be improved with a little intake with the conventional hemoferrum goods.

[0042]

[Effect of the Invention]By this invention, the hemoferrum content oral composition in which internal absorption is carried out effectively is provided.

Appendix

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